REMARKS

Claims 1-18 and 21-29 are currently pending in this application. According to the Office Action mailed on May 1, 2008, claims 1-18, 28, and 29 have been examined on their merits and have been objected to and/or rejected. Claims 21-27 have been withdrawn as directed to non-elected subject matter.

Applicants have amended claim 28. No new matter has been added to the application by this amendment. In view of the amendment and the remarks below, Applicants respectfully request that the objection and rejections asserted in the Office Action be reconsidered and withdrawn.

OBJECTION TO CLAIM 28

Claim 28 has been objected to because of the parentheses around "(t-PA)". Claim 28 has been amended to delete the parentheses. Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1-18, 28, and 29 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action contends that the specification does not teach what encompasses the "advising" step.[1] Applicants respectfully traverse this rejection because the specification recites that the method comprises "engaging the subject in exercise training for a period of time sufficient to increase fibrinolysis levels in the subject,"[2] or "placing the subject on a regimen of extensive, moderate, or limited exercise for a time sufficient to alleviate or prevent cardiovascular disease."[3]

Under 35 U.S.C. § 112, first paragraph, a specification must describe the invention with sufficient detail so that one of ordinary skill in the art would conclude that the inventor had possession of the claimed invention. MPEP § 2163; *Lockwood v. American Airlines, Inc.*, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The detail required to comply with

[1] Office Action at page 3.
[2] Specification at ¶ 6.
[3] Specification at ¶ 25.

the written description requirement is that the specification makes the claimed invention obvious. *Univ. of Cal. v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1405 (Fed. Cir. 1997).

Here, one of ordinary skill in the art would understand from the recitation of "engaging the subject" or "placing the subject" on an exercise regimen that the inventors had possession of "advising" the subject to exercise. After all, in practice, the subject would be asked or advised to participate in an exercise regimen.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

I. PREVIOUSLY ASSERTED RESPONSE

Claims 1-18, 28, and 29 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.[4] At page 6, the Office Action contends that while "the specification asserts that there is a tendency for subjects with 4G/4G genotypes to respond better than subjects with 4G/5G or 5G/5G genotypes (paragraph [0048]), the analysis of the data (P ANOVA) indicates that none of the changes are statistically significant".

Applicants respectfully traverse this rejection and disagree with this contention because, as evidenced by the Kulaputana et al. article,[5] the data in Table 1 contains statistically significant data. A copy of the Kulaputana et al. article is submitted with this amendment.

The Kulaputana et al. article, authored by the inventors among others, discusses the same experiments and reports the same data as set forth in Example 6 of the present application. Table 2 in the article corresponds to the data reported in Table 1 of this application. Likewise, Table 3 in the article corresponds to the data reported in Table 2 of this application.

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[4] Office Action at pages 4-13.
[5] Kulaputana *et al.*, "Genetic Markers of Fibrinolytic Responses of Older Persons to Exercise Training", INT'L J. OF SPORTS MED. (2006) 27: 617-622.

The Kulaputana et al. article discloses that statistically significant changes in t-PA antigens after exercise were observed when the test subject had at least one PAI-1 4G allele. The article reports that for individuals genotyped as 4G/4G, there was a -1.0 ± 0.3 changes in t-PA antigen levels after the subjects exercised. This change is reported as statistically significant because it has a p-value of less than 0.01. The article reports that, for individuals genotyped as 4G/5G, there was a -0.9 ± 0.3 change in t-PA antigen levels. This change is also reported as statistically significant because it has a p-value of less than 0.05. Therefore, the article evidences that there are statistically significant changes in t-PA antigen levels in individuals, carrying at least one PAI-1 4G allele who exercise. Claims 1-18 relate to this statistically significant change in t-PA antigen levels when a person having at least one PAI-1 4G allele exercises.

The Kulaputana et al. article also discloses that the inventors observed statistically significant changes in t-PA activity when a subject was homozygous for the PAI-1 4G allele. Table 2 in the article reports that the observed change in t-PA activity in 4G/4G individuals who exercised was 0.38 ± 0.11. The article reports that this change is statistically significant because it has a p-value of less than 0.01. Therefore, the article provides further evidence that the specification recites stastically significant changes in t-PA activity in individuals carrying two copies of the PAI-1 4G allele who exercise. New claims 28 and 29 relate to this stastically significant change in t-PA activity after exercise when a person has two copies of the PAI-1 4G allele.

At page 6, the Office Action further contends that the "specification does not provide any data concerning any sort of control group, for example a reference group that did not participate in an exercise program." Applicants respectfully disagree with this contention because the specification provides baseline data for the subjects examined, which represents t-PA activity and t-PA antigen levels prior to exercising. The baseline data was taken after the subjects completed the screening, dietary stabilization, and prior to commencing the exercise program. This is the control because it represents the t-PA activity and t-PA antigen levels of subjects consuming diet according to the experimental procedure and who have not exercised.

At page 6, the Office Action further contends that there is no indication that improving fibrinolysis or alleviating symptoms of cardiovascular disease were measured.

Directly measuring improved fibrinolysis or alleviating symptoms of cardiovascular disease is not necessary because, as the specification recites, there is a link connecting t-PA activity and t-PA antigen levels with improved fibrinolysis (see specification at paragraphs [0012], [0024], and [0050]). There is also a link connecting improved fibrinolysis with alleviated symptoms of cardiovascular disease (see specification at paragraphs [0003] and [0007]). According to MPEP § 2107, the Examiner must accept statements of fact made by the applicant as true. By accepting these facts as true, the specification provides data that fibrinolysis was improved and that symptoms of cardiovascular disease were alleviated in subjects with at least one 4G allele who engaged in exercise, because the specification establishes that increased t-PA activity or decreased t-PA antigen improves fibrinolysis, and thereby alleviates symptoms of cardiovascular disease.

Likewise, the specification also establishes that limited or extensive exercise will also improve fibrinolysis, and thereby, alleviate symptoms of cardiovascular disease. At paragraph [0050], the specification states that "endurance training, whether that training is extensive, moderate, or limited, increases fibrinolysis ...." Again, accepting this as true, which must be done in the absence of evidence to the contrary, the specification enables one skilled in the art to make and use the claimed invention with any level of exercise.

II. RESPONSE TO OFFICE ACTION OF MAY 1, 2008

On page 11, the Office Action acknowledges that the data provided in the specification is statistically significant. However, it contends that "this data is not reconciled with the data presented in the cited Tiyasangthong thesis." According to the precedent set forth in *Ex parte D'Antonio*, Appeal No. 1998-1987, Application No. 07/915,783, 2001 WL 35825743 (BPAI 2001), Applicants respectfully disagree.

In *D'Antonio*, the examiner rejected the claims under 35 U.S.C. § 112, first paragraph, as not enabled by the specification. 2001 WL 35825743 at *4. Specifically, the examiner concluded that the data was insufficient to enable the claims, and cited references that questioned the validity of the experimental systems used. *Id.* The Board reversed the rejection because statistically significant results are sufficient to establish utility (utility rejections are, at times, incorrectly phrased as enablement rejections). *Id.* at *5, quoting *In re*

Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995), citing *In re Krimmel*, 292 F.2d , 953 (CCPA 1961).

In the instant specification, Applicants have demonstrated statistically significant results. Accordingly, in view of *D'Antonio*, reconsideration and withdrawal are respectfully requested.

REJECTION UNDER 35 U.S.C. § 102

Claims 1-18, 28, and 29 have been rejected under 35 U.S.C. § 102(b) as anticipated by Väisänen.[6]

I. THE RECITED INVENTION

Claims 1, 7, and 13 are directed to methods of decreasing the level of t-PA antigen; preventing cardiovascular disease; or ameliorating cardiovascular disease respectively. The methods comprise identifying at least one 4G allele and/or genotype at the plasminogen activator inhibitor-1 (PAI-1) gene promoter site in the subject, and advising the subject to engage in exercise training for a period of time sufficient to decrease the level of t-PA antigen. Claims 2-6 depend from claim 1. Claims 8-12 depend from claim 7. Claims 14-18 depend from claim 13. Claim 28 is directed to a method of increasing the level of t-PA activity in a human subject. The method comprises identifying two 4G alleles and/or genotype at the plasminogen activator inhibitor-1 (PAI-1) gene promoter site in the human subject, and advising the human subject to engage in exercise training for a period of time sufficient to increase the level of t-PA activity. Claim 29 depends from claim 28.

In summary, the claims share the following common limitations – identifying at least one 4G allele and/or genotype at the PAI-1 gene and advising the subject to exercise to decrease t-PA antigen or increase t-PA activity.

II. THE CITED REFERENCES

Väisänen discloses identifying subjects having 4G/4G, 4G/5G, and 5G/5G genotypes.[7] It does not disclose advising a subject having at least one 4G allele at the PAI-1 gene to exercise to decrease t-PA antigen or increase t-PA activity.

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[6] Väisänen *et al.*, "Regular exercise, plasminogen activator inhibitor-1 (PAI-1) activity and 4G/5G promoter polymorphism in the PAI-1 gene," THROMB. HAEMOST (1999) 82: 1117-1120.

III. ANALYSIS

For a reference to anticipate a claimed invention, the reference must teach each and every limitation recited in the claim. Väisänen fails to disclose all of the recited elements because it fails to teach advising a subject having at least one 4G allele at the PAI-1 gene to exercise to decrease t-PA antigen or increase t-PA activity. Therefore, Väisänen does not anticipate the recited invention, and reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments to the claims and remarks, Applicants respectfully submit that the specification and claims are in condition for allowance. Accordingly, reconsideration and withdrawal of the asserted objections and rejections, and allowance of pending claims 1-18, 28, and 29, are respectfully requested. Rejoinder of withdrawn claims 21-27 is also requested.

Respectfully submitted,

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[7] Väisänen at page 1118.